Stereoselective Interaction of Benzopyrano[3,4-b][1,4] Oxazines with P-glycoprotein

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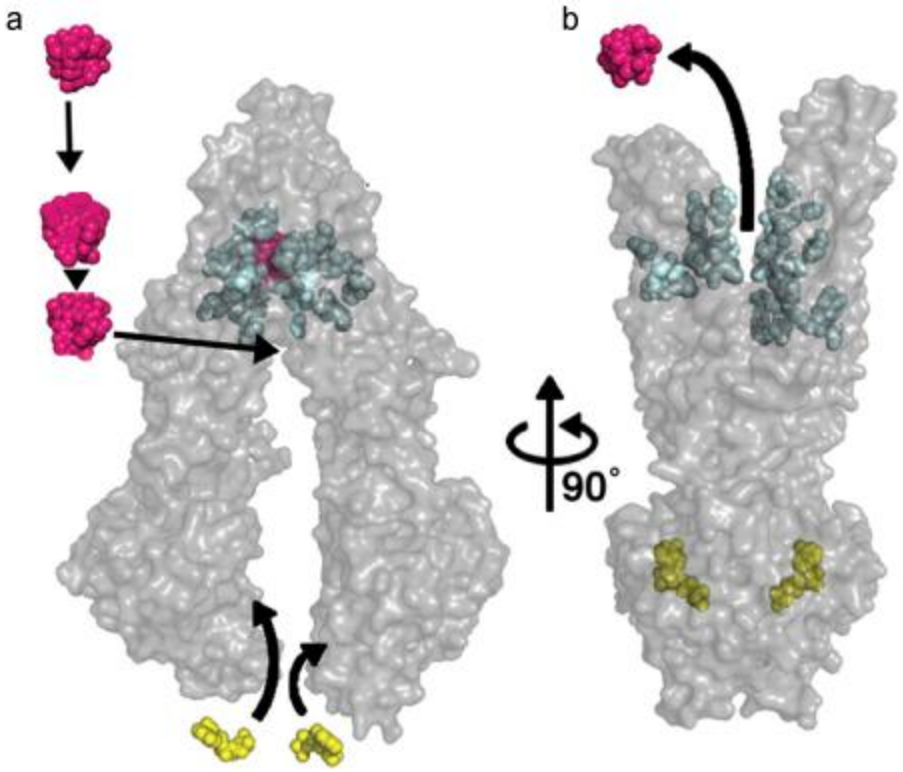
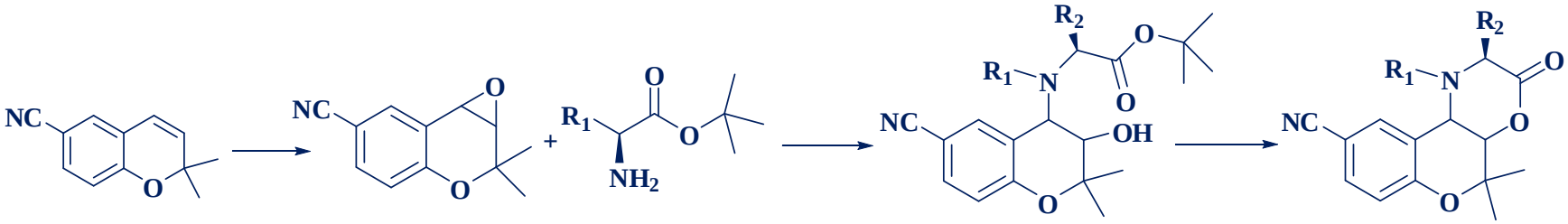
P-glycoprotein (P-gp)

- A transmembrane, ATP dependent drug efflux pump
- 2 Transmembrane domains
- 2 ATP-binding sites
- Hydrophobic vacuum cleaner
- Intestine, liver, kidney
- Blood-brain-barrier
- Tumors
- Polyspecific ligand recognition
- Limited stereoselectivity

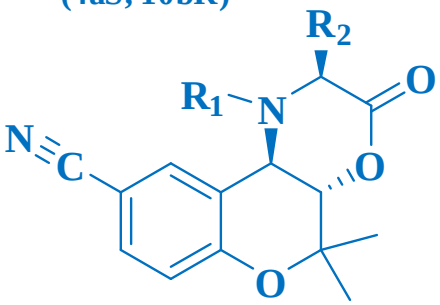


Stereoselective Ligands Database

Benzopyrano[3,4-b][1,4] Oxazines

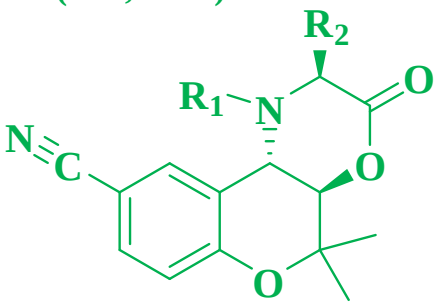


(11-13a)
(4aS, 10bR)



Class (a)

(11-13b)
(4aR, 10bS)



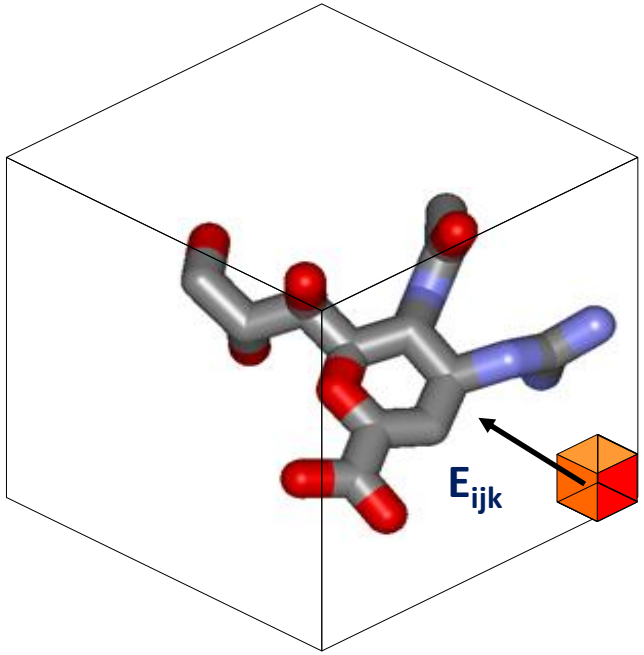
Class (b)

R1 = CH_3 , H

R2 = -CH_3, -$CH(CH_3)_2$, -$CH(C_6H_5)$

GRID Independent Descriptor Analysis (GRIND)

- This strategy does not require that the compounds in the training series share a common scaffold

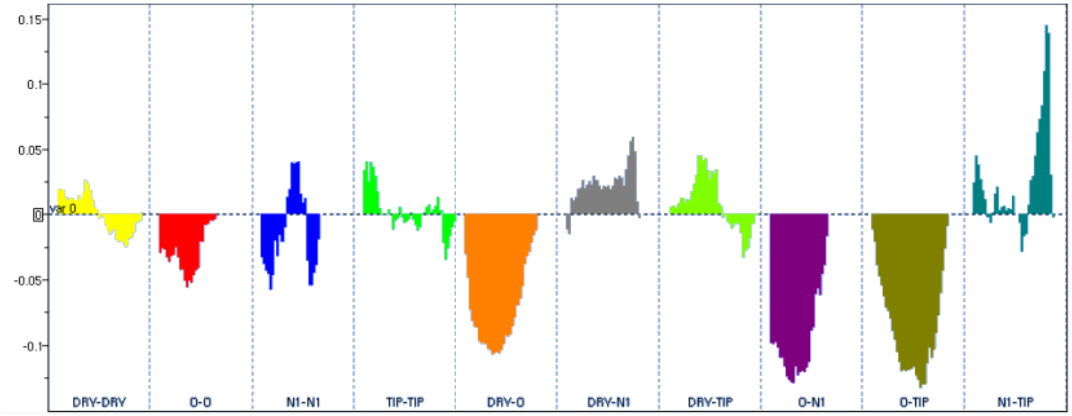


- The MIF can be obtained by sampling the space at regular intervals with a probe and computing the molecule-probe energy of interaction

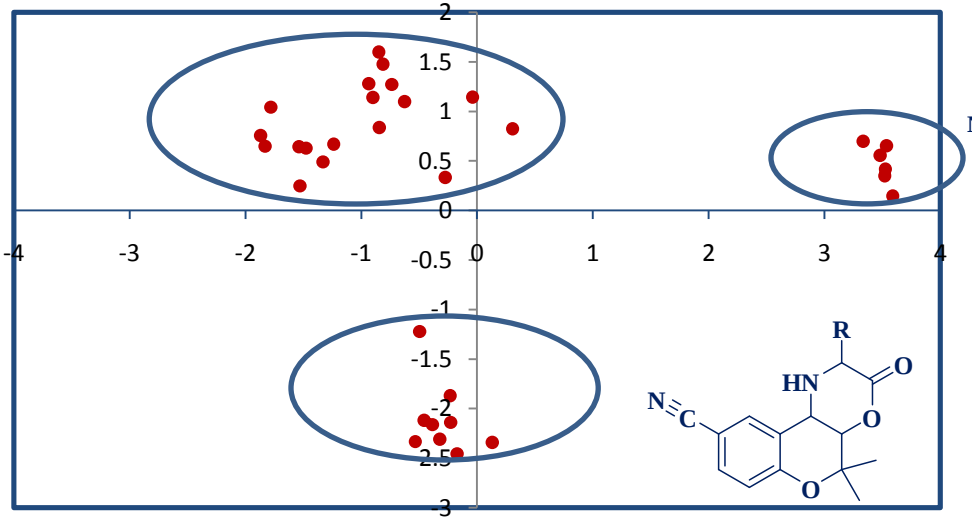
$$E_{ijk} = \sum E_{LJ} + \sum E_{EL} + \sum E_{HB}$$

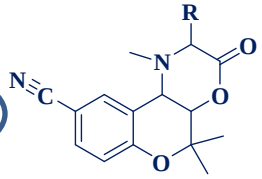
- MIF Computation = GRID
  Probes = Dry, TIP, N1, O
  Discretization = AMANDA
  Encoding= MACC2

Principle Component Analysis (PCA)



PC1

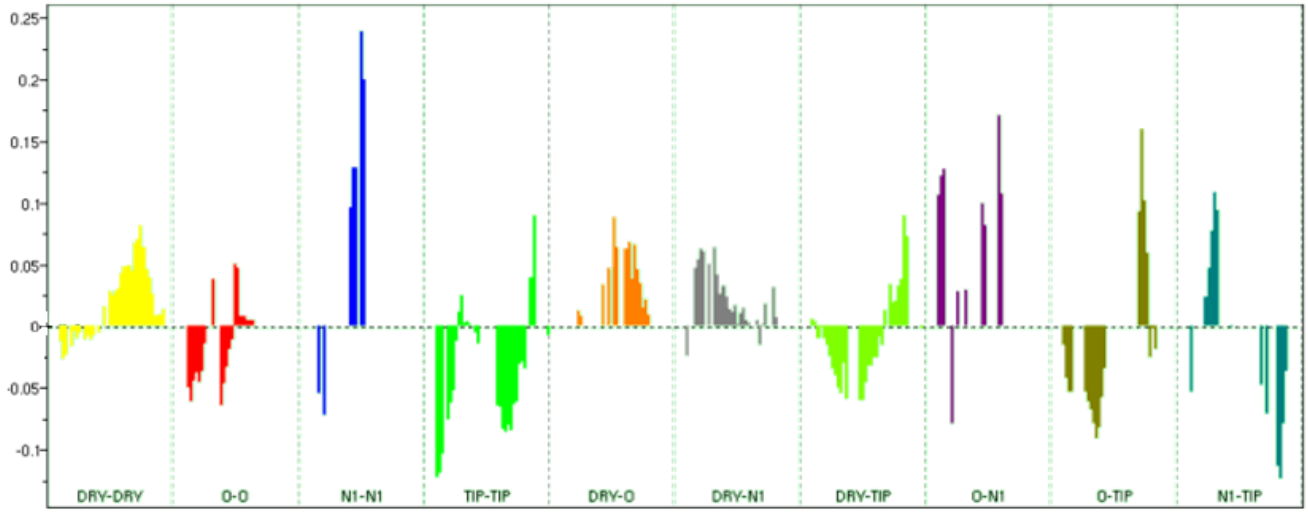




PC2

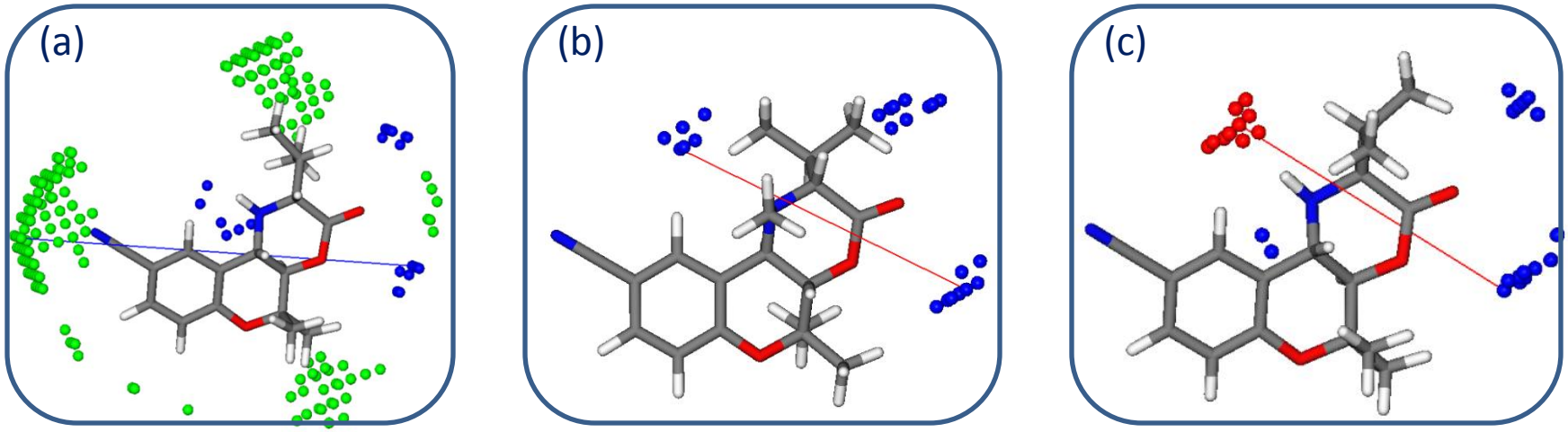
Partial Least Square Analysis (PLS)

$q^2 = 0.61$; $R^2 = 0.80$; SDEP= 0.50



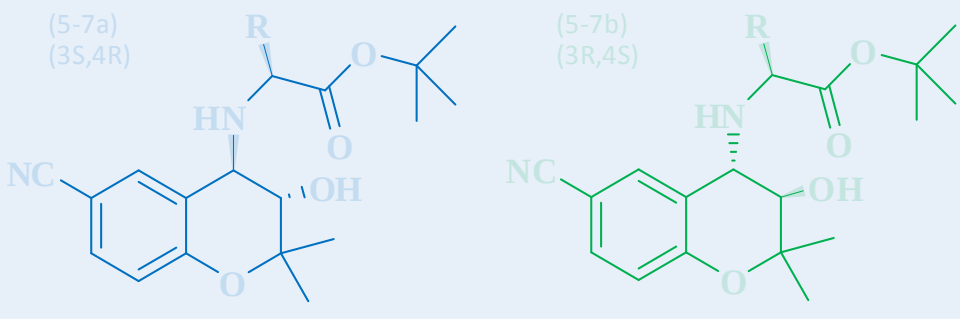
The PLS Coefficient correlograms showing the descriptors, which are directly (positive value) or inversely (negative values) correlated to the activity. The activity particularly increases with the increase in (N1-N1), (O-N1) and (O-TIP)descriptor value

GRIND Interpretation



- (a): N1-TIP (Shape and H-bond donor descriptor) More distance between two probs leads to decrease in activity
- (b): N1-N1 (H-bond donor descriptors) two H-bond acceptors at a distance of 8.80-9.20 Å contribute positive to the activity
- (c): O-N1 (H-bond donor and acceptor descriptors) at a distance of 8.00-8.4 Å contribute positive to the activity

Structure Activity Relationship (SAR)

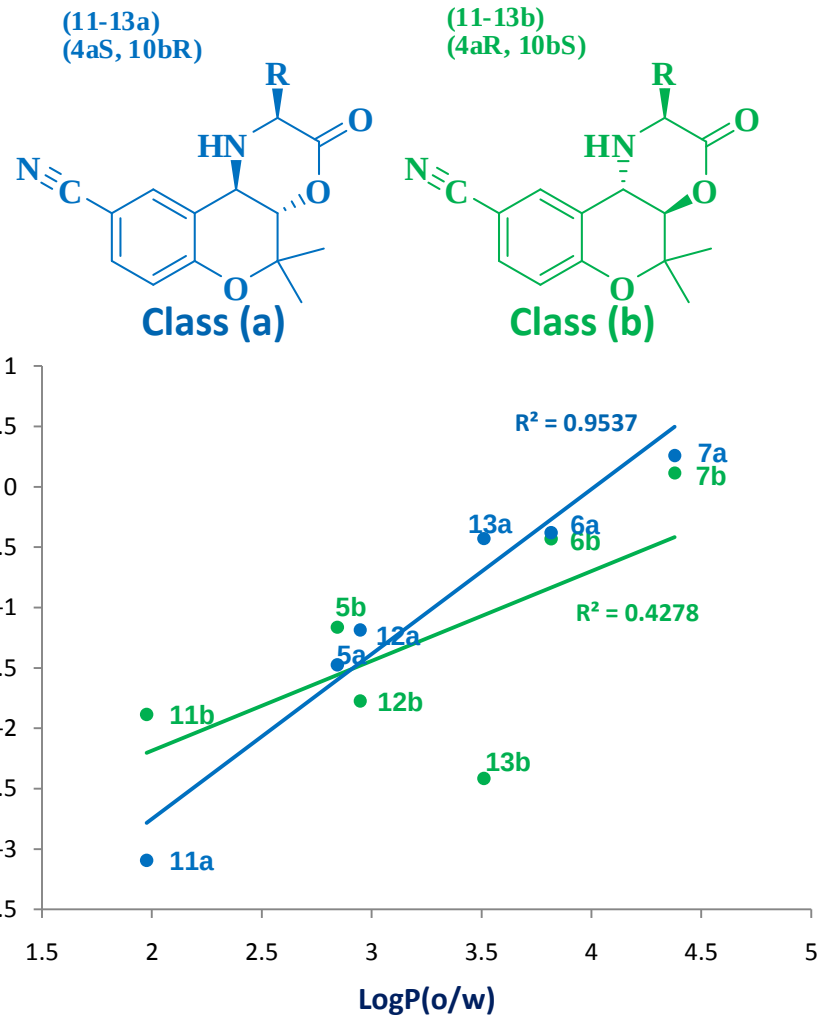


- EC_{50} values cover a range of more than three order of megnitude
- For all three diasterioisomeric pairs almost no difference in biological activity
- The pattern change remarkably upon ring closure to benzopyrano[3,4-b][1,4]oxazines

#	R	Log P	EC_{50} (μM)
5a	CH_3	2.84	29.85
5b	CH_3	2.84	14.55
6a	$CH(CH_3)_2$	3.82	2.40
6b	$CH(CH_3)_2$	3.82	2.70
7a	$CH_2(C_6H_5)$	4.38	0.55
7b	$CH_2(C_6H_5)$	4.38	0.77
11a	CH_3	1.98	1241.65
11b	CH_3	1.98	76.89
12a	$CH(CH_3)_2$	2.95	15.32
12b	$CH(CH_3)_2$	2.95	59.33
13a	$CH_2(C_6H_5)$	3.51	2.69
13b	$CH_2(C_6H_5)$	3.51	259.78

Lipophilicity and P-gp inhibitory activity

- Within (a) series of compounds differences in their P-gp inhibitory potency are mainly due to their capability to permeate into the membrane bilayer
- Remarkable drop of activity for the benzyl-derivative (**13b**) strongly indicates steric constraints for (b) series and thus maybe leading to different binding modes at P-gp



Homology Modeling and Docking

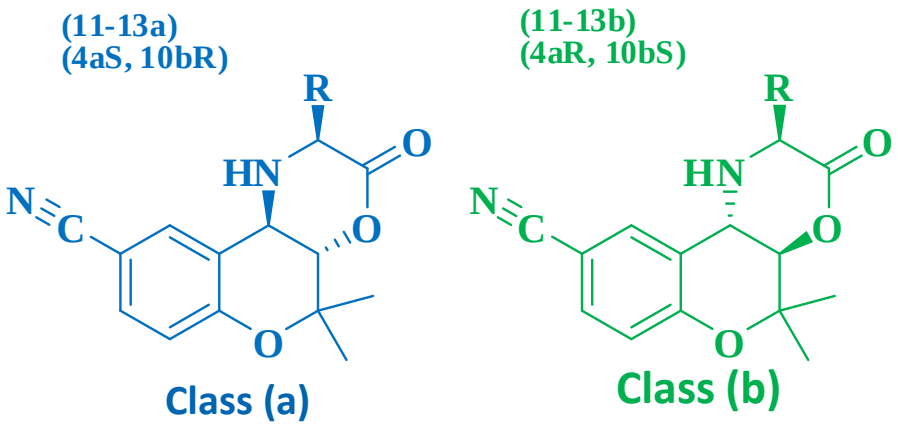
Template

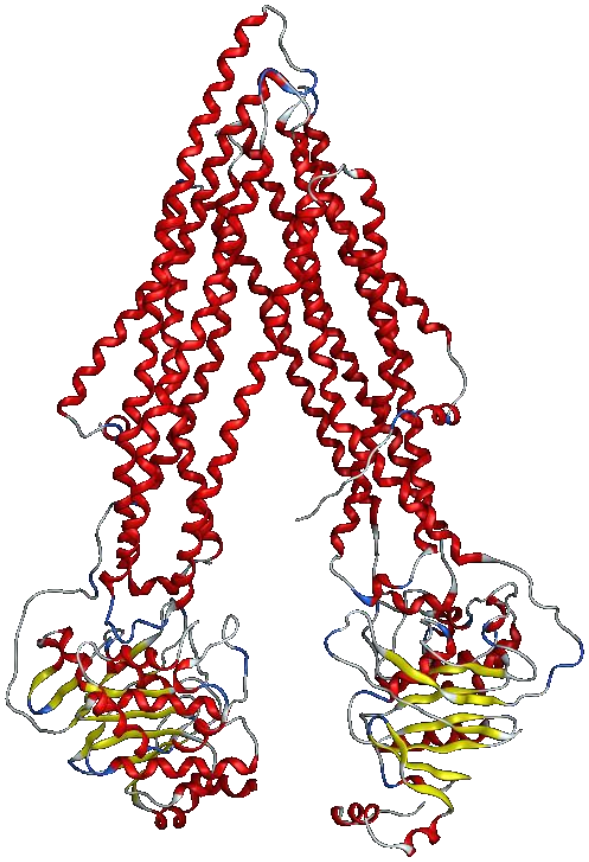
PDB: 3G5U – chain A

Alignment

Proposed by Aller et al. (2009)

Docking

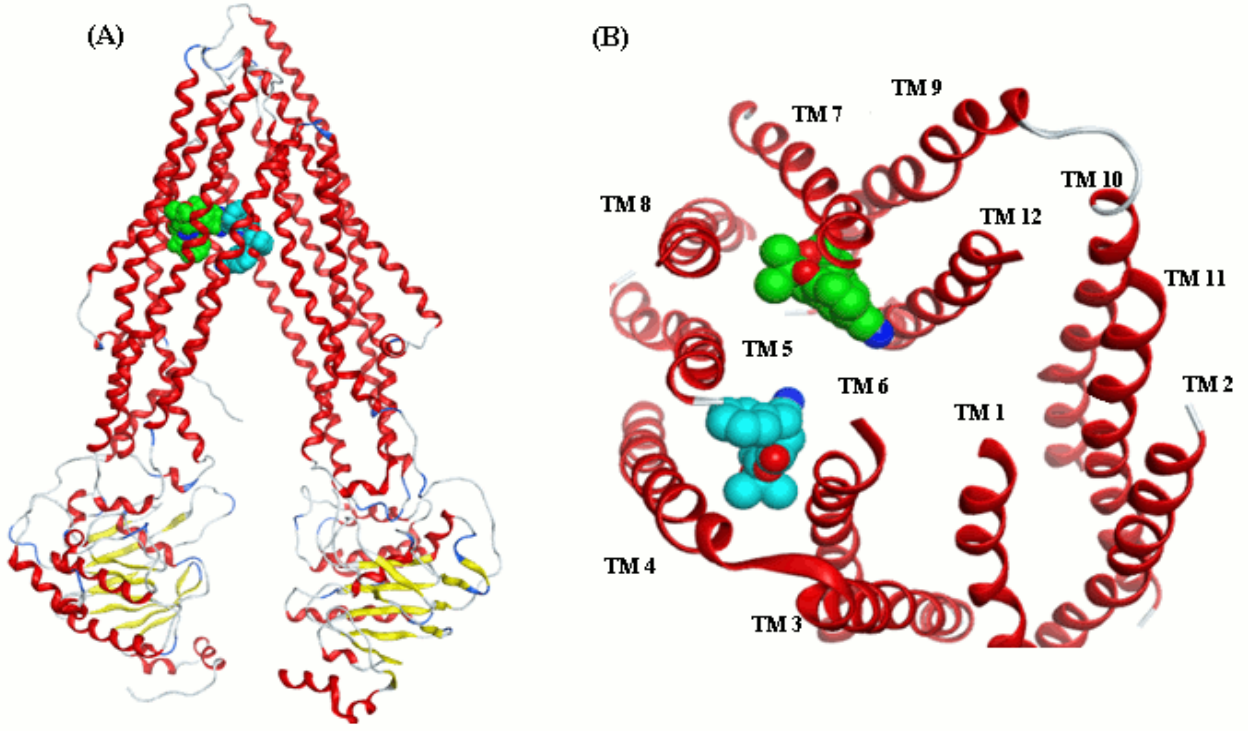




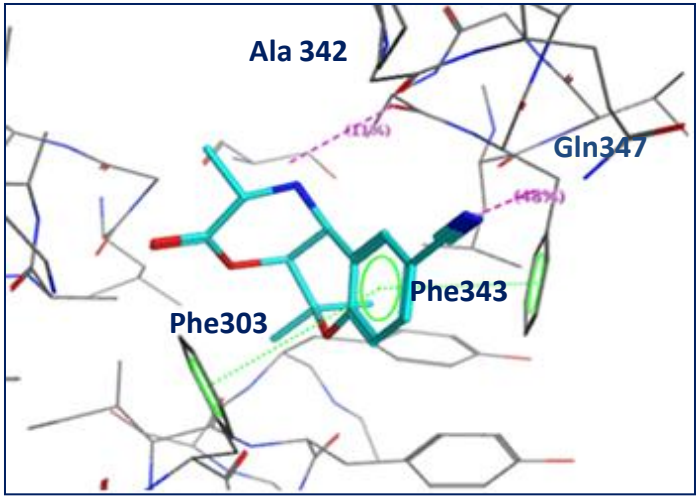
R = -CH_3, -$CH(CH_3)_2$, -$CH(C_6H_5)$

Common Scaffold Clustering

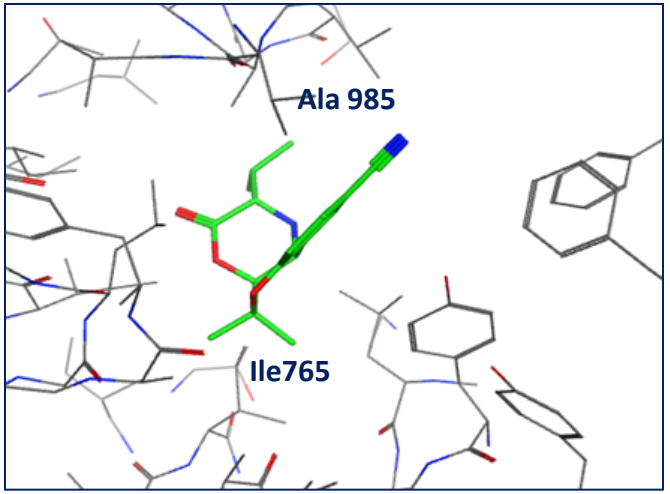
- Seven clusters contain only (a) type of compounds
- Eight clusters contain all compounds of type (b)



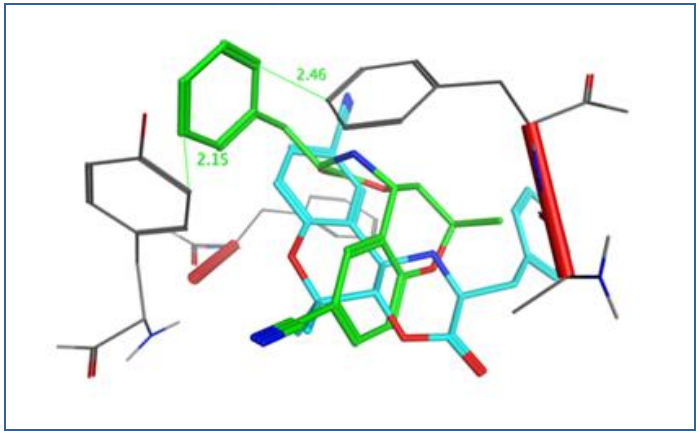
Ligand-Protein Interaction



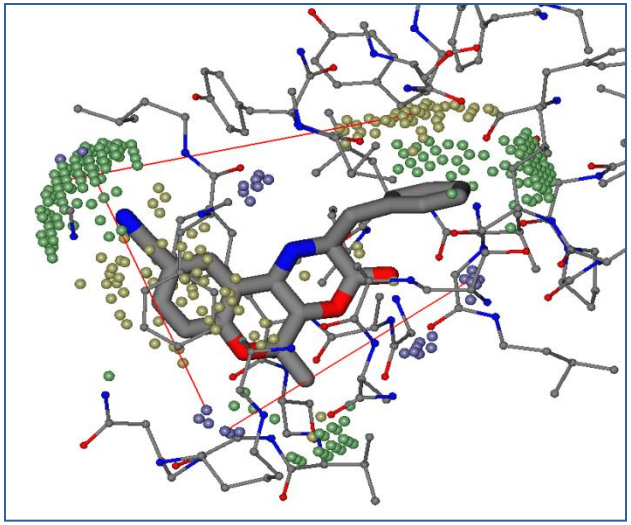
11b



12b



13a and b



Conclusions

- ✓ The pharmacophore consists of two H-bond-acceptor groups, one H-bond donor; shape of the molecules also plays a major role in the interaction
- ✓ Two H-bond acceptors at a distance of 8.8 -9.4 Å contribute positively to the activity of inhibitors
- ✓ TM4, 5, 6, 7, 8 and 12 are involved in the ligand protein interaction of P-gp
- ✓ Best scored poses of both classes of compounds show interactions with amino acid residues Phe303, Phe343, Ala342, Gln347 and Tyr307
- ✓ Only compounds of class (b) additionally show hydrophobic interaction with Ala985 and lle765

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